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Associated Factors of Tophaceous Gout: A Study Involving 20 Primary Care Clinics in an Urbanized State in Malaysia

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ABSTRACT

Objectives: Gout is a treatable disease. A complication of untreated or poorly-controlled gout is tophi formation. We conducted this study to investigate the associated factors of tophaceous gout among patients who attended 20 primary care clinics in Selangor, an urbanized state in Malaysia. ***Methods***: We conducted a cross-sectional study from July to October 2019 that included all patients with gout who attended the clinics. Data on clinical demographics and laboratory results were collected. Comparison between tophaceous and non-tophaceous groups was performed using descriptive analysis. ***Results:*** A total of 421 patients with gout were involved in this study, 83 (19.7%) patients had visible tophi and were categorized into the tophaceous group, while the other 338 (80.3%) patients were categorized into the non-tophaceous group. The majority of patients were male with a mean age of 57.6±12.8 years. Three factors found to be significantly associated with tophaceous gout were age at symptom onset [tophaceous (45.6±13.3 years) vs. non-tophaceous (49.7±13.9 years), $p = 0.026$], mean disease duration of gout [tophaceous (105.2±92.6 months) vs. non-tophaceous (77.6±88.6 months), $p = 0.013$], and baseline serum uric acid level [tophaceous (622.3±129.1 μmol/L) vs. non-tophaceous (582.6±102.3 μmol/L), $p = 0.021$]. ***Conclusions:*** Tophaceous gout is associated with longer disease duration, higher baseline serum uric acid level, and younger age at symptoms onset. Hence, early initiation of urate-lowering therapy with a treat-to-target approach is crucial to prevent tophi formation.

Gout is a common form of inflammatory arthritis characterized by the deposition of monosodium urate crystals in the synovial fluid of joints and other tissues.[1] The 2017 Global Burden of Disease reported an increasing prevalence and incidence of gout in recent years worldwide, including in Southeast Asia.[2] The age-standardized prevalence and annual incidence rates in Southeast Asia in 2017 were 449.3 and 88.5 cases per 100 000 population, respectively.[2] Despite being a treatable disease,[1] there was an increase in aged-standardized years lived with disability rate with 14 cases per 100 000 persons in 2017.[2]

One of the complications of untreated or poorly-controlled gout is tophi formation, which is a consequence of long-standing hyperuricemia.[1,3] It can lead to joint deformity, chronic pain, and functional disability, and seriously impact patients' quality of life. The recommended target serum uric acid (sUA) level in the presence of tophi is < 300 μmol/L,[4,5] which is lower compared to non-tophaceous gout. Several factors associated with tophaceous gout have been studied and identified.[6,7] However, most studies on gout were conducted in developed countries. We conducted this study to investigate the factors associated with tophaceous gout in primary care settings in an urbanized state in a developing country.[8]

METHODS

We conducted a cross-sectional study in 20 government primary care clinics from July to October 2019. Patients diagnosed with gout by the

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primary care doctors that attended the clinics during the study period were included.

Patient's characteristics (gender, ethnicity, age, age of symptoms onset, duration of gout, family history, smoking history, presence of tophi, comorbidities, height, and weight) and laboratory data (baseline sUA and current serum creatinine) were collected. The presence of tophi was determined through physical examination by the primary care doctors. Body mass index was calculated by dividing the weight in kilograms by the height in meters squared. Creatinine clearance was calculated using the Cockcroft-Gault formula.

Statistical analysis was performed with SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Descriptive statistics were used to describe the clinical variables. The patients were divided into two groups, tophaceous and non-tophaceous groups. Comparison between the two groups were analyzed using chi-square and Fisher's exact test for categorical variables and student's *t*-test for continuous variables. A significant *p*-value was set at < 0.05. From our data, percentage of missing variables ranged from 0.5–37.8%. The highest proportion of missing variables were baseline estimated glomerular filtration rate (eGFR) and baseline sUA. Written consent was taken from all patients. Ethical approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia (ID: NMRR-18-3290-45183).

RESULTS

A total of 421 gout patients participated in this study. The majority (90.4%) were male. The mean

Table 1: Comparison between tophaceous and non-tophaceous groups.

Variables	Patients n	Tophaceous n (%)	Non-tophaceous n (%)	*p*-value
Gender	419			
Male	350	75 (90.4)	275 (81.8)	0.061#
Female	69	8 (9.6)	61 (18.2)	
Ethnic group	415			
Malay	319	63 (75.9)	256 (77.1)	0.816#
Non-Malay	96	20 (24.1)	76 (22.9)	
Age, mean ± SD, years	417	56.7 ± 12.4	57.8 ± 12.9	0.458*
Age at symptom onset, mean ± SD, years	353	45.6 ± 13.3	49.7 ± 13.9	0.026*
Disease duration, mean ± SD, months	415	105.2 ± 92.6	77.6 ± 88.6	0.013*
Family history of gout	408			
Yes	139	33 (41.8)	106 (32.2)	0.108#
No	269	46 (58.2)	223 (67.8)	
Comorbidities	421			
Hypertension	341	66 (79.5)	275 (81.8)	0.701#
Hyperlipidemia	281	49 (59.0)	232 (68.6)	0.096#
Diabetes mellitus	184	33 (39.8)	151 (44.7)	0.468#
Ischemic heart disease	42	6 (7.2)	36 (10.7)	0.347#
Heart failure	11	0 (0.0)	11 (3.3)	0.132$
Stroke	15	3 (3.6)	12 (3.6)	1.000$
BMI, mean ± SD, kg/m^2	389	29.5 ± 5.2	30.1 ± 5.9	0.450*
Baseline sUA, mean ± SD, µmol/L	262	622.3 ± 129.2	582.6 ± 102.3	0.021*
Recent eGFR, mean ± SD, mL/min/1.73m^2	262	59.3 ± 25.8	65.0 ± 35.6	0.789*
≤ 60	151	33 (61.1)	118 (56.7)	0.562#
> 60	111	21 (38.9)	90 (43.3)	
On Allopurinol	411			
Yes	310	67 (80.7)	243 (74.1)	0.090#
No	101	16 (19.3)	85 (25.9)	

BMI: body mass index; sUA: serum uric acid; eGFR: estimated glomerular filtration rate.
**p-values were calculated using Student's t-test; #chi-square test; $Fisher's exact test.*
Due to missing data, the percentage or mean was calculated based on available data for each variable.

age was 57.6±12.8 years, ranging between 23 and 89 years. The mean age of symptoms onset was 48.9±13.8 years, while the mean disease duration was 82.9±89.9 months. Of 415 patients who declared their ethnicity, 75.9% were Malay. The most frequent comorbidities found among 421 patients were hypertension in 341 (81.0%), hyperlipidemia in 281 (66.7%), and diabetes mellitus in 184 (43.7%).

Eighty-three (19.7%) patients were categorized into the tophaceous group, while the other 338 (80.3%) patients were categorized into the non-tophaceous group. The mean age of gout symptom onset was earlier in the tophaceous group compared to the non-tophaceous group (45.6±13.3 years vs. 49.7±13.9 years, $p = 0.026$). The mean disease duration of gout was also longer in the tophaceous group compared to the non-tophaceous group (105.2±92.6 months vs. 77.6±88.6 months, $p = 0.013$). The percentage of patients with comorbidities such as hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, and stroke were similar between the two groups.

Baseline sUA levels were available in 262 (62.2%) patients (49 tophaceous and 213 non-tophaceous). The mean baseline sUA was higher in tophaceous compared to the non-tophaceous group (622.3±129.2 μmol/L vs. 582.6±102.3 μmol/L, $p = 0.021$). Calculation of current eGFR was performed for 262 patients (54 tophaceous and 208 non-tophaceous) whose serum creatinine was available. Of 262 patients, 151 (57.6%) had eGFR of ≤ 60 mL/min/1.73m^2; of 151, 33 (21.9%) were in tophaceous group and 118 (78.1%) were in the non-tophaceous group. The comparison of mean eGFR between these two groups was similar [Table 1].

DISCUSSION

Our study was conducted in government primary care clinics in Selangor, an urbanized and the most populous state in Malaysia, to investigate the factors associated with tophaceous gout. Tophus is an organized chronic inflammatory granulomatous state in response to monosodium urate crystals, in which both innate and adaptive immune systems are involved.[1] Prolonged hyperuricemia state may lead to tophi formation as a consequence of tissue or joint deposition of uric acid. In our cohort, sUA level was found to be significantly higher in tophaceous group, which was parallel with findings in the Chinese, European, and USA cohort.[6,7]

In this study, patients with tophaceous gout developed gout symptoms at a younger age compared to patients with non-tophaceous gout. Similarly, Ma et al[6] also reported a younger age of symptom onset in patients with tophaceous gout, although this association became non-significant after multivariate analysis.[6] An observational study showed no association between early- and late-onset gout in tophi formation.[9] However, large cohort studies identified that longer gout duration was significantly associated with tophi formation,[6,7] which was consistent with our study. Interestingly, this association was not seen in a community-based study in New Zealand,[10] a country with the highest prevalence and incidence of gout globally.[2]

Several studies had demonstrated that the elderly or older age group was associated with tophaceous gout,[7,10,11] which was not found in our study. This may be due to the earlier initiation of urate-lowering therapy in our cohort. There are controversial results between the association of tophaceous gout and cardiovascular disease (CVD). Gancheva et al[12] reported that tophaceous gout was associated with the progression of arteriosclerotic-type vessel changes using carotid doppler US, compared to asymptomatic hyperuricemia and non-tophaceous gout. On the other hand, Dalbeth et al[10] reported no significant difference in CVD when comparing tophi and non-tophi gout patients. In the current study, we did not find any significant difference in either CVD or CV risk factors, including obesity, between tophaceous and non-tophaceous gout. These can be explained by the high prevalence of CV risk factors, specifically diabetes mellitus, hypertension, and obesity in the Malaysian population, regardless of gout diagnosis.[13–15]

More importantly, although no significant differences in CV risk factors were found between tophaceous and non-tophaceous gout, there was a higher prevalence of CV risk factors among our gout patients compared to the general population,[16] which was parallel with other studies.[17,18] Based on the National Health and Morbidity Survey 2019,[16] the prevalence of hypertension, diabetes mellitus, obesity, and hyperlipidemia among the Malaysian population were 30.0%, 18.3%, 33.7%, and 38.1%, respectively. In our patient cohort, the prevalence of hypertension, diabetes mellitus, obesity, and hyperlipidemia were 81.0%, 43.8%, 62.5%, and 66.7% respectively.

Renal impairment is associated with hyperuricemia due to under excretion of uric acid.[19] This may lead to a higher uric acid burden, which predisposes to tophi formation. Some studies had reported chronic kidney disease as a risk factor for gouty tophi,[7,10,12] although a Chinese cohort study showed a different result.[6] The presence of multiple comorbidities, which contributed to renal impairment in both tophaceous and non-tophaceous gout in this study, may explain the absence of significant association between eGFR levels and presence of tophi.

A genetic polymorphism in association with tophaceous gout was reported in a Taiwanese study in 2008.[20] Interestingly, a higher percentage of positive family history was observed in the tophaceous compared to non-tophaceous group (41.8% vs. 32.2%) in our study, although analysis had shown no significant association. The same result was observed in the study by Ma et al.[6]

This is the first study involving the participation of 20 primary care clinics in Selangor, the most populous state in Malaysia with a population of 6.57 million.[21] Hence, these data could represent the real-world data gout status in an urbanized city or region, in a developing country such as Malaysia. A prevalence study would be beneficial to investigate gout epidemiology, including the socioeconomic burden of gout.

One limitation of this study is that the data collected was based on medical records and patients' recollections, and prone to recall bias. We also did not investigate alcohol as a variable because three-quarters of patients in our study were of Malay ethnicity, which is predominantly Muslim, who may not reveal their alcohol intake willingly. Lastly, 37.8% of data on the baseline creatinine level was missing, which may have affected the result of the current chronic kidney disease status. We did not report on smoking history because of missing data, and we believe the reason was that many patients were not forthcoming with their smoking history.

CONCLUSION

Longer gout duration, higher baseline sUA, and younger age at symptom onset are predictors of tophaceous gout in this study. We would like to stress the importance of starting patients on urate-lowering therapy early with a treat-to-target approach to reduce the duration of hyperuricemia state that may potentially lead to tophi formation. Although there are no differences in the comorbidities between the tophaceous and non-tophaceous groups, the prevalence of these co-morbidities in our patients was higher compared to the general population, therefore CV risk factors screening should be emphasized and managed accordingly.

Disclosure

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